Equivalence in clinical assessment of iron status requires ferritin assay standardisation before harmonisation of ferritin reference intervals

In their Article, Judy Truong and colleagues summarise ferritin reference intervals from published literature and the five most commonly used commercial ferritin assays,[1] and found large variation in the lower reference limit, despite evidence suggesting that a ferritin of less than 30 µg/L is a sensitive and specific cutoff for the diagnosis of iron deficiency. Bias in reference intervals is attributed to improper patient inclusion and inadequate adherence to reference interval establishment standards. However, the authors did not mention the most important obstruction of a universal reference interval for ferritin: shortcomings in standardisation of ferritin assays.

Uncertainty of ferritin cutoff in clinical decision making can be attributed to two main causes. First, cutoffs for the diagnosis of iron deficiency in guidelines are often based on the systematic review by Guyatt and colleagues,[2] and cite older studies that have various forms of heterogeneity and bias, including population differences. To address this bias, we and other researchers and clinicians (including Truong and colleagues) have expressed the need for additional research to establish (functionally) relevant ferritin cutoff values for iron deficiency on the basis of rational, evidence-based research.[1] Several studies in young, apparently healthy women of reproductive age have addressed this need with functional readouts of body iron status (ie, beginning of upregulation of iron absorption, increase of soluble transferrin receptor, zinc protoporphyrin, and decrease in haemoglobin) to define the lower ferritin reference limit to diagnose iron deficiency.[3]

Second, several lines of evidence show ferritin assays are not optimally harmonised or standardised. This shortcoming in assay standardisation might also have contributed to bias in the aforementioned systematic review by Guyatt and colleagues and studies that functionally defined ferritin cutoff concentrations to define iron deficiency.[2,3] Since the early 1980s, WHO has developed four different preparations of reference material to improve comparability between ferritin assays.[4,5] However, these preparations have insufficient traceability to each other, causing substantial variation between assays calibrated with different generations of these reference materials.[4,5] Moreover, recent studies suggest WHO reference materials might not be optimally commutable (ie, might show other interassay differences than native human samples, precluding standardisation).[5] To illustrate the problem, the Dutch organiser for external quality assessment schemes, SKML, showed in their proficiency tests in the Netherlands that ferritin concentrations measured in one and the same human serum sample (fresh frozen pooled) had interassay differences of up to 50% (Thelen M, unpublished [communication on confidential SKML external quality assessment reports, 2020 to current]).

We conclude that establishment of a universal ferritin reference interval is not possible until all commercial ferritin assays are metrologically traceable to the same well-defined and commutable standard. Only then will a universal ferritin reference interval result in equivalent result interpretation and patient classification.

MT is the director of SKML, a non-profit organisation that provides external quality assurance schemes that include ferritin, with method grouping acording to metrological traceability. SKML is paid by participants and has no financial relationship with any commercial organisation related to ferritin assays. SKML's only interest in this Correspondence is in expressing its external quality assessment judgement of ferritin that is professional objective judgement based on metrological traceability from SKML. All other authors declare no competing interests.

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Radiotherapy for haematological malignancies

Radiotherapy for haematological malignancies has undergone substantial changes over the past few decades.[1] Due to advances in imaging and radiation treatment technology, improvements in our biological understanding of these diverse cancers, and developments in systemic therapies, radiation has become in